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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,560	02/09/2001	Marianne Harboe	58982.000002	6162

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Stanislaus Aksman
Hunton & Williams
Suite 1200
1900 K Street, N.W.
Washington, DC 20006

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,560	HARBOE, MARIANNE	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,9-14,16-18,29-31,35,36,39 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,9-14,16-18,29-31,35,36,39 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42 are pending in the application.

[2] Applicants' amendment to the claims, filed August 09, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicants' arguments filed August 09, 2004 have been fully considered.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[5] The use of the trademarks "Hannilase™, "Thermolase™," and "Modilase™" has been noted in this application (p. 15). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

[6] In view of applicants' amendment to the claims, the objections to claims 12 and 15 as set forth in items [6] and [7], respectively, of the Office action mailed February 09, 2004 are withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

[7] Claim(s) 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[8] Claims 1 (claims 5-6, 9-12, 18, 29-31, 35-36, 39, and 42 dependent therefrom), 13-14, and 16-17 are indefinite in the recitation of "about" regarding a pH value. It is unclear to the examiner as to the range of pH values that are intended by the term "about." For example, is the term "a pH... ... about 2.0" meant to encompass a pH value of 2.01? 2.1? 3? Applicants are requested to clarify the meaning of the term "about" in the context of a pH value.

Claim Rejections - 35 USC § 112, First Paragraph

[9] Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 (claims 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42 dependent therefrom) recites the limitation "subjecting said medium to a pH between about 1.8 and about 2.0 for a period of time of at least 2.5 hours" (claim 1, part (ii)) and claims 13-14 and 16-17 further limit the pH range. MPEP 2163 states, "with respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims." In the amendment filed August 08, 2004, applicants specifically direct the examiner's attention to page 13, lines 1-2; page 15, lines 6-8, and original claims 6-8 for support for the amended claims. However, the examiner can find no support for the limitations stated above at page 13, lines 1-2; page 15, lines 6-8, or original claims 6-8. The examiner *can* find support for the following limitation: subjecting commercial microbial products to a pH of 1.7 for 2.5 hours (page 15, lines 6-7). Applicants are invited to direct the examiner's attention to the specification, claims, and/or drawings as originally filed wherein specific support for the limitation as stated above can be found.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[10] Claim(s) 1, 5-6, 9-10, 13-14, 16-18, 29-31, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Uren et al. (US Patent 4,721,673). The claims are drawn to a method of providing a milk composition comprising the active steps of providing a medium having a pH of 2.0 or greater comprising chymosin and glucoamylase and subjecting said medium to a pH between about 1.8 and about 2.0 for at least 2.5 hours to inactivate at least 50% of the glucoamylase activity while maintaining at least 85% of the chymosin activity.

Uren et al. teach a method for activating and purifying *E. coli* expressed bovine chymosin by solubilizing the expressed prochymosin, renaturing the prochymosin, conversion of the prochymosin to active chymosin by incubation in a buffer at about pH 2.0 for a period of time of 4 hours (column 6) or three days (column 7), followed by purification of the chymosin using ammonium sulfate precipitation (columns 4-5). This anticipates claims 1, 5-6, 9-10, 13-14, 16-18, 29-31, and 35 as written.

It should be noted that Uren et al. do not provide data indicating that, after practicing their method, one of ordinary skill would have inactivated at least 50% or 90% of the *E. coli* glucoamylase activity while maintaining at least 85% of the recombinant chymosin activity. However, this is an inherent feature of practicing the method of Uren et al.

Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA

1977) and *In re Fitzgerald* et al., 205 USPQ 594. It should be noted that any admission by applicant that the method of Uren et al. would not generate the desired level of active chymosin/inactive glucoamylase may be used by the examiner in a scope of enablement rejection under 35 USC 112, first paragraph.

[11] It is noted that the specification fails to specifically define the term "medium," however, the specification discloses that "[i]t will be appreciated that any starting material or intermediate material that is applied in the manufacturing of a preparation containing a desired polypeptide as well as the final product as such can be subjected to the treatment at low pH" (p. 6, bottom). Also, the American Heritage Dictionary (1992) meaning of the term "medium" is "[a]n intervening substance through which something else is transmitted or carried on." Thus, in accordance with MPEP 2111, the term "medium" has been provided its broadest reasonable interpretation, including resuspended cellular debris comprising prochymosin as taught by Uren et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[12] Claim(s) 1, 5-6, 9-14, 16-18, 29-31, 35-36, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ward et al. (*Biotechnol* 8:435-440; cited in the IDS filed April 16, 2001) in view of Uren et al., Li et al. (*Biochem Biophys Acta* 1384:121-129) and Pedersen et al. (*Eur J. Biochem* 94:573-580). The claims are drawn to a method of providing a milk clotting composition as described above.

The recombinant expression of chymosin using prokaryotic and eukaryotic microorganisms was well known in the art at the time of the invention. For example, Ward et al. teach *Escherichia coli*, *Saccharomyces cerevisiae*, and *Yarrowia lipolytica* have been used successfully as host cells for the recombinant expression of prochymosin cDNA (page 435, right column, middle). Ward et al. teach recombinant expression of prochymosin as a fusion in these host cells yielded increased intracellular or extracellular expression (page 435, right column). Ward et al. teach a vector encoding a glucoamylase-bovine prochymosin B fusion protein for recombinant expression in Aspergillus niger var. awamori (page 435, abstract). Ward et al. teach that following expression and secretion of the fusion protein into the Aspergillus niger var. awamori culture medium, treatment at pH 2.0 for thirty minutes released the glucoamylase from the chymosin (page 435, middle). Ward et al. teach treatment of the Aspergillus niger var. awamori culture medium at pH 2.0 caused a shift from prochymosin to a size suggestive of pseudochymosin (p. 438, left column, bottom). Ward et al. do not teach exposing the Aspergillus niger var. awamori culture medium

comprising the chymosin-glucoamylase fusion protein to pH 2.0 for at least 2.5 hours.

At the time of the invention, the activation of chymosin by treatment of prochymosin at an acidic pH was well known in the art. See the teachings of Uren et al. as stated above. Also, Li et al. teach activation of bacterially expressed prochymosin by exposure of the prochymosin at pH 2.0 for 2-14 hours to convert the prochymosin to pseudochymosin (p. 123) following the method of Pedersen et al.

Pedersen et al. teach that activation of prochymosin at pH 2.1 as measured by milk-clotting activity increases with time (p. 578, Figure 2). The results of Pedersen et al. indicate that maximum activation of prochymosin due to acidic pH treatment occurs around 4 hours.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Ward et al., Uren et al., Li et al., and Pedersen et al. to practice the method for activating the prochymosin-glucoamylase fusion protein of Ward et al. at pH for a time of at least 4 hours in order to obtain maximum activation of the prochymosin-glucoamylase fusion protein. One would have been motivated to practice the method for activating the prochymosin-glucoamylase fusion protein of Ward et al. at pH for a time of at least 4 hours in order to obtain maximum activation of the prochymosin-glucoamylase fusion protein because of the teachings of Li et al. and Pedersen et al. as described above. One would have a reasonable expectation of success for practicing the method for activating the prochymosin-glucoamylase fusion protein of Ward et al. at pH for a time of at

least 4 hours because of the results of Ward et al., Uren et al., Li et al., and Pedersen et al. Therefore, claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, and 42, drawn to a method of providing a milk clotting composition as described above would have been obvious to one of ordinary skill in the art.

[13] Claim(s) 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ward et al. in view of Uren et al., Li et al., and Pedersen et al. as applied to claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, and 42 above, and further in view of Kappeler et al. (US Patent Application Publication 2002/0164696 A1; cited in the Office action mailed February 09, 2004). Claim 39 limits the method to a *Camelus dromedarius* chymosin.

Ward et al., Uren et al., Li et al., and Pedersen et al. disclose the teachings as stated above. The references do not teach a *Camelus dromedarius* chymosin.

Kappeler et al. teach the isolation of a nucleic acid encoding *Camelus dromedarius* chymosin and recombinant expression thereof using *Aspergillus niger* var. *awamori* as an expression host (see Examples 1-3). Kappeler et al. teach that a comparison of the clotting activities of camel and bovine chymosins reveals that camel chymosin has 170-180% of the clotting activity of bovine chymosin with less non-specific proteolytic activity than bovine chymosin (see Example 5).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Ward et al., Uren et al., Li et al., and Pedersen et al. and Kappeler et al. to practice the method of Ward et al. for expressing a

glucoamylase-camel chymosin fusion protein and treating the resulting culture medium to pH 2.0 for at least 4 hours. One would have been motivated to practice the method of Ward et al. for expressing a glucoamylase-camel chymosin fusion protein and treating the resulting culture medium to pH 2.0 for at least 4 hours in order to obtain camel chymosin for use in milk clotting/cheese production and to achieve maximum activation of the prochymosin. One would have a reasonable expectation of success to practice the method of Ward et al. for expressing a glucoamylase-camel chymosin fusion protein and treating the resulting culture medium to pH 2.0 for at least 4 hours because of the teachings of Ward et al., Uren et al., Li et al., and Pedersen et al. and Kappeler et al. as described above. Therefore, claim 39, drawn to the method described above would have been obvious to one of ordinary skill in the art.

[14] It should be noted that the combined references do not provide data indicating that, after practicing the method of Ward et al. modified by treating the resulting culture medium to pH 2.0 for at least 4 hours, one of ordinary skill would have inactivated at least 50% or 90% of the glucoamylase activity while maintaining at least 85% of the recombinant chymosin activity. However, this is an inherent feature of practicing the method of Ward et al. modified by treating the resulting culture medium to pH 2.0 for at least 4 hours.

Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA

1977) and *In re Fitzgerald* et al., 205 USPQ 594. It should be noted that any admission by applicant that the method of Ward et al. practiced using a time of 4 hours or greater would not generate the desired level of active chymosin/inactive glucoamylase may be used by the examiner in a scope of enablement rejection under 35 USC 112, first paragraph.

[15] Applicants' arguments addressing the rejections under 35 U.S.C. 103(a) in the Office action mailed February 09, 2004 are acknowledged. However, in view of the amendment to the claims, the previous rejections under 35 U.S.C. 103(a) have been withdrawn in favor of the new rejections stated above. It is noted that the withdrawal of the previous rejections is not due to applicants' arguments. In view of the withdrawal of the previous rejections under 35 USC 103(a), applicants arguments are moot.

Conclusion

[16] Status of the claims:

- Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42 are pending.
- Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the

status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1652
09-28-04